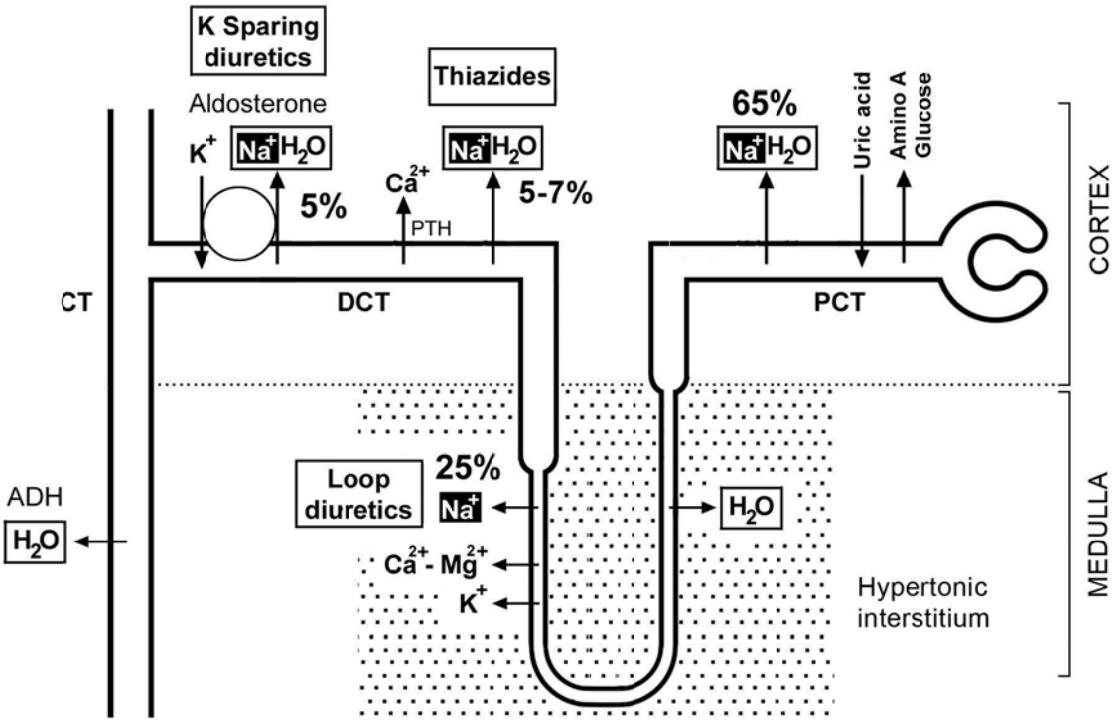
Diuretic Agents and Volume Balance

Part 1: Basic information

TUBULAR FUNCTION AND URINE FORMATION

- The renal blood flow (RBF) is **1.1 L /min** (~ 22% of COP).
- The glomerular filtration rate (GFR) is **125 ml/min.**
- The capillary tuft filtrates ~ 180 L of fluid per day. 99% of the filtered fluid is reabsorbed again during passage in the renal tubules.
- Water reabsorption is usually **2ry to Na^+ reabsorption** (except in the collecting tubules; 'CT'). Any drug that ↓ Na^+ reabsorption (= ↑ Na^+ loss), also ↓ water reabsorption (= ↑ water loss or 'diuresis').



Tubular reabsorption and sites of action of 3 types of diuretics

- **Proximal convoluted tubules (PCT):**
  - **Reabsorption:** (75% of the glomerular filtrate).
    - Active reabsorption of Na^+ **(~65%).**
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
    - Reabsorption of all filtered K^+, glucose, amino acids, and drugs.
  - **Secretion:** active secretion and reabsorption of organic acids and bases into tubular fluid.

- **Loop of Henle (LOH):**
  - **Descending limb:** passive reabsorption of water due to hypertonicity of the medullary interstitium.
  - **Ascending limb:** active reabsorption of Na^+ **(~25%)** (this causes hypertonicity of the medullary interstitium), Ca^{2+} and Mg^{2+}.

- **Distal convoluted tubules (DCT):**
  - **Proximal part:**
    - Active reabsorption of Na^+ **(5-7%).**
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
    - Active reabsorption of **Ca^{2+}** (under the influence of **parathormone 'PTH'**).
  - **Distal part:**
    - Active reabsorption of Na^+ **(2–5%)** in exchange with K^+ (under the influence of **aldosterone**).
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.

- **Collecting tubules (CT):** Reabsorption of water under the influence of **ADH.**

EDEMA AND EDEMATOUS CONDITIONS

- Edema is defined as the accumulation of fluid in the interstitial space due to either:
  - Increased capillary hydrostatic pressure
  - Decreased plasma oncotic pressure.
  - Increased capillary permeability.
- Edema can be either **exudative** (having high protein content) or **transudative** (having low protein content).
- **Exudative edema** results from increased capillary permeability as part of the acute inflammatory response. It is usually localized to the site of inflammation and will not be considered in this chapter.

- **Transudative edema** is usually generalized and is associated with renal Na^+ retention. The three most common clinical causes are:
  - **Congestive heart failure (CHF):** the decreased COP causes renal ischemia which stimulates the renin-angiotensin-aldosterone system (RAAS) → Na^+ and water retention → edema.
  - **Liver cirrhosis:** the cirrhotic liver cannot synthesize sufficient albumin and other plasma proteins → ↓ plasma oncotic pressure. Hypoalbuminemia together with portal hypertension and 2ry stimulation of RAAS cause fluid retention (edema) and accumulation of fluid in the peritoneal cavity (ascites).
  - **Nephrotic syndrome:** glomerular dysfunction causes excessive loss of plasma proteins in urine → ↓ plasma oncotic pressure → edema.

Part 2: Diuretic classes and agents

Diuretics are drugs that increase urine volume and Na^+ excretion.
Natriuretic: a drug that increase Na^+ excretion by the kidney.

Classification of diuretics:

Renal diuretics	Extra-renal diuretics
They act directly on the kidney: ■ **Thiazide diuretics:** act on the proximal part of the DCT *e.g. hydrochlorothiazide.* ■ **Loop diuretics:** act on the ascending limb of loop of Henle *e.g. furosemide.* ■ **K^+ sparing diuretics:** act on the distal part of the DCT *e.g. spironolactone.* ■ **Osmotic diuretics:** substances that ↑ the osmotic pressure of tubular fluid → ↓ water reabsorption by renal tubules *e.g. mannitol.*	They act indirectly on the kidney: ■ **Water diuresis:** ↑ water intake → ↓ ADH release → diuresis. ■ **Digitalis in CHF:** ↑ the COP leading to ↑ RBF → diuresis. ■ **i.v. albumin in ascites or nephrotic edema:** to increase plasma osmotic pressure → mobilization of edema fluid toward the vascular compartment → ↑ RBF → diuresis.

N.B. Carbonic anhydrase inhibitors *e.g acetazolamide*: they are weak diuretics that ↓ $NaHCO_3$ reabsorption from the PCT and may cause **metabolic acidosis**. They also ↓ aqueous humor secretion and can be used in the treatment of glaucoma (see pharmacology of the eye).

Loop diuretics

(Furosemide, torsemide, bumetanide , and ethacrynic acid)

Pharmacokinetics

- They are absorbed from the GIT and secreted into the lumen of the PCT by an organic acid excretory system.
- The absorption of furosemide is erratic but bumetanide is complete.
- Diuresis occurs within **5** minutes after i.v. administration and within **30** minutes of oral administration.

Mechanism and pharmacological effects

- Loop diuretics **inhibit $Na^+/K^+/2Cl^-$ co-transport** system in the thick ascending limb of LOH leading to inhibition of the active reabsorption **Na^+**, **Cl^-**, and **K^+**. These ions are excreted with equiosmotic amount of **water**.
  - They also increase **excretion** of **Ca^{2+}**, **Mg^{2+}**, **halides** and **H^+**.
  - Na^+ and water loss at this segment is high, so they are **potent (or high ceiling)** diuretics (i.e., up to 25% of the filtered Na^+ load).
- They ↑ **renal PGE2 and PGI2** production leading to **VD** and ↑ RBF and GFR.
  - Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit PG synthesis and antagonize this effect of loop diuretics.
  - VD of **pulmonary** vascular bed also occurs due to ↑ PG formation.

Therapeutic uses

- **Edematous conditions:** e.g. CHF, nephrotic syndrome, etc.
  - Many patients require fluid and sodium restriction to have the best results.
  - Diuretics are **not used** to treat edema due to lymphatic obstruction (lymphedema) or inflammatory edema (localized edema with high protein content is difficult to be resolved by diuretics).
- **Acute pulmonary edema:** loop diuretic ↓ pulmonary congestion by:
  - They cause venodilatation → ↓ venous return.
  - They cause VD of pulmonary vascular bed even before diuresis occurs.
- **Acute renal failure:** to maintain adequate GFR and enhance K^+ excretion.
- Acute **hypercalcemia** and acute **hyperkalemia**: saline should be given to compensate for Na^+ and water loss.
- **Hypertensive emergencies:** i.v. furosemide is usually given in emergencies:
  - Loop diuretics ↓ plasma volume.
  - They cause peripheral VD due to ↑ PGs production in many vascular beds.
  - Hyponatremia ↓↓ sensitivity of the vascular smooth muscles to circulating catecholamines.

Adverse effects

- **Hypovolemia** and **hypotension.**
- **Electrolyte disturbances:** Hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia (all need to be properly replaced).
- **Hypokalemic metabolic alkalosis:** due to ↑ tubular secretion of K^+ and H^+.
- **Hyperuricemia** and precipitation of acute gout: This is caused by:
  - Increased uric acid reabsorption in the PCT as a result of hypovolemia (It may be prevented by using lower doses to avoid hypovolemia).
  - Competition with uric acid excretion at the organic acid excretory system in the PCT.
- **Ototoxicity:**
  - It is **reversible** hearing loss. It occurs with very **high** doses.
  - It may be due impairment of **ion transport** in the stria vascularis (inner ear).
  - Occurs more frequent with:
    - Patients with impaired renal function.
    - Ethacrynic acid.
    - Concomitant use of other ototoxic drugs e.g. aminoglycosides.
- **Allergic reactions:** all loop diuretics (except ethacrynic acid) are derivatives of sulfonamides; they cause occasional skin rash, eosinophilia, and less often, interstitial nephritis.

Thiazide diuretics

Classification

- **True thiazides** (they are derivatives of sulfonamides): hydrochlorothiazide, bendroflumethiazide.
- **Thiazide-like diuretics:** metalozone, indapamide, chlorthalidone.

Pharmacokinetics

- Thiazide diuretics are absorbed from the GIT. They are secreted into the lumen of the PCT by an organic acid excretory system.
- They produce diuresis within 1–2 hours.

Mechanism and pharmacological effects

- Thiazides **inhibit Na^+/Cl^- co-transport** system in the proximal part of **DCT** leading to inhibition of the active reabsorption **Na^+**, **Cl^-**. These ions are excreted with equiosmotic amount of **water**.
  - Excess **Na^+** reaching the DCT is reabsorbed in exchange with **K^+** (→ **K^+ loss).**

- They also increase **excretion** of **halides** and **H^+**.
- They ↓ **Ca^{2+} excretion** and enhance its reabsorption.
- Thiazides have **moderate efficacy** (i.e., maximum excretion of filtered Na^+ load is only 5-7%).
- Most thiazides are ineffective if the GFR is < 30-40 ml/min (so it is not useful, or even harmful, in presence of renal failure).

- The action of thiazides also depends on **renal PGs** like loop diuretics but to much less extent.

Therapeutic uses

- **Mild edematous states:** cardiac, hepatic, or renal (same as loop diuretics).
- **Essential hypertension** (mild to moderate)**:**
  - They have the same mechanisms like loop diuretics (mention them).
  - They are often combined with other antihypertensive drugs to enhance their blood pressure-lowering effects.
- **Hypercalcuria and renal Ca^{2+} stones:** to ↓ urinary **Ca^{2+}** excretion.
- **Nephrogenic diabetes inspipidus (DI):**
  - Thiazides can reduce urine volume in some cases of DI. This is called **"paradoxical antidiuretic action"** and it is not clearly understood. It may be due to improvement of ADH receptor sensitivity in the renal collecting tubules.

Adverse effects

- **Hypovolemia** and **hypotension.**
- **Electrolyte disturbances:** Hyponatremia and hypokalemia.
- **Hypokalemic metabolic alkalosis:** due to ↑ tubular secretion of K^+ and H^+.
- **Hyperuricemia** the same as with loop diuretics.
- **Hyperglycemia:** due to both ↓ pancreatic release of insulin and ↓ tissue utilization of glucose.
- **Hyperlipidemia:** due to ↑ cholesterol and LDL (by 5-15%).
- **Allergic reactions:** thiazides are derivatives of sulfonamides; they cause occasional skin rash, dermatitis, and less often, thrombocytopenia.

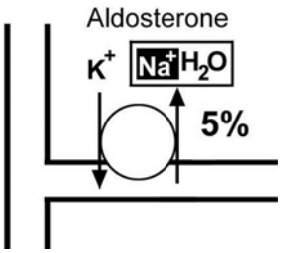
Potassium-sparing diuretics
(Spironolactone – triameterine – amiloride)

- Spironolactone is a **steroid** congener of aldosterone.
- Triamterene and amiloride are synthetic drugs **but not steroids.**

Pharmacokinetics

- All are absorbed from the GIT.
- Spironolactone and triamterene are metabolized by the liver
- Amiloride is excreted unchanged in the urine.
- They have **slow onset** (days).

Mechanism and pharmacological effects



- **Site of action:** the distal part of the DCT where Na^+ is reabsorbed (**2–5%**) in exchange with K^+ under the influence of **aldosterone**.
- **Spironolactone** is a competitive antagonist of aldosterone at its receptor site at the distal part of DCT leading to ↑ Na^+ excretion (with excretion of equiosmotic amount of water) and K^+ retention.
- **Triamterene and amiloride** are **direct inhibitors** of Na^+ channels in the distal part of DCT leading to ↑ Na^+ excretion (with excretion of equiosmotic amount of water) and K^+ retention.

- **The net effect is:**

– Mild Na^+ and water loss (i.e., maximum excretion of filtered Na^+ is only 2-5%)
– Hyperkalemia: due to ↓ K^+ excretion (K^+ will be retained in blood).
– Metabolic acidosis: due to ↓ H^+ ion excretion (H^+ will be retained in blood).

Therapeutic uses

- **All cases of edema due to hyperaldosteronism:**
  - Primary hyperaldosteronism: e.g. Conn's disease.
  - Secondary hyperaldosteronism: e.g. in liver cirrhosis or nephrotic syndrome.
- **Used in combination with loop diuretics or thiazides in order to:**
  - To minimize the risk of electrolyte imbalance:
    Loop diuretics cause hypokalemia while K^+ sparing diuretics cause hyperkalemia. Their combination can minimize electrolyte disturbance.
  - To minimize the risk of acid-base imbalance:
    Loop diuretics cause metabolic alkalosis while K^+ sparing diuretics cause metabolic acidosis. Their combination can minimize acid-base imbalance.
  - To make synergism in cases of refractory (resistant) edema.
- **Treatment of female pattern hair loss**:

  Spironolactone is a weak competitive inhibitor of **androgens** at their receptors and ↓ synthesis of testosterone (antianderogenic effect). Some dermatologists use this feature to stop androgen-related frontal hair loss in women.

Adverse effects

- **Hyperkalemia** due to ↓ K^+ excretion.
- **Hyperkalemic metabolic acidosis:** due to ↓ K^+ and ↓ H^+ excretion.
- Spironolactone has **antiandrogenic effects** (gynecomastia and impotence in males).

N.B.

Eplerenone is a similar congener of spironolactone. It has little antiandrogenic effects but more hyperkalemic effects.

Contraindications

- **All cases of hyperkalemia:** especially in the following conditions:
  - Patients with chronic renal failure.
  - With drugs that cause hyperkalemia e.g. ACEIs.
- **Spironolactone should not be given with carbenoxolone** because carbenoxolone has aldosterone-like action and can antagonize the effect of spironolactone.

	Spironolactone	Triamterene - amiloride
Structure	Synthetic steroid	Synthetic non-steroids
Metabolism	Extensive metabolism in the liver	Amiloride is excreted unchanged in urine
Mechanism of action	Competitive antagonism with aldosterone at its receptor site in the DCT	Direct inhibition of Na^+ channels at the distal part of DCT
Antianderogenic efcts	Gynecomastia & impotence	Not present

Osmotic diuretics: Mannitol, Glycerol

They are chemically inert substances given by **i.v. infusion** in **emergency** conditions

Mechanism of action

- First, they ↑ osmotic pressure of plasma leading to withdrawal of transcellular fluid (e.g. aqueous humor, excessive CSF, etc).
- Second, they are freely filtered by the glomerulus and ↑ osmotic pressure of the tubular fluid leading to ↓ water reabsorption by renal tubules.

Therapeutic uses

Acute congestive glaucoma and acute rise in intracranial pressure: they are given by i.v. infusion for rapid ↑ drainage of of aqueous humor or CSF respectively by increasing the osmotic pressure of the plasma before diuresis begins.

Adverse effects: dehydration with hypernatremia is the main adverse effect.

Comparison between the 3 main classes of diuretics

	Loop diuretics	Thiazides	K+ sparing diuretics
Site of action	thick ascending limb of LOH	proximal part of DCT	distal part of DCT
Mechanism	Inhibit $Na^+/K^+/2Cl^-$ co-transport system	inhibit Na^+/Cl^- co-transport system	Spironolactone is a competitive antagonist of aldosterone Triamterene and amiloride are direct inhibitors of Na^+ channels in the distal part of DCT
Efficacy	High	Moderate	Mild
Onset	Rapid (minutes)	Less rapid (hours)	Slow (days)
Serum K+	Hypokalemia	Hypokalemia	Hyperkalemia
Blood pH	Metabolic alkalosis	Metabolic alkalosis	Metabolic acidosis
Ca2+ excretion	↑	↓	--
Use in renal failure	Can be used	Not effective or harmful	Contraindicated
Use in hypertension	Hypertensive emergencies	Mild essential hypertension	In combination with other diuretics
Blood glucose	Little or no effect	Rise	Little or no effect
Plasma lipids	Little or no effect	Rise	Little or no effect
Ototoxicity	Common	Less common	Rare

Part 3: Advantages and disadvantages of diuretics in some edematous conditions

CONGESTIVE HEART FAILURE (CHF)

Patients with CHF have ↓COP due to weak cardiac muscle, fluid retention, and lung congestion. Many patients have also high blood pressure.

Advantages of diuretics:

- Correction of fluid retention.
- Lowering of blood pressure.
- Decrease preload (venodilatation and ↓ venous return) and afterload (due to arterial VD) leads to improvement of cardiac contraction.
- Decrease lung congestion causes improvement of tissue oxygenation.
- Recent evidence showed that **spironolactone** reduces morbidity and mortality rates in patients with advanced heart failure.

Disadvantages of diuretics:

- Excessive hypovolemia can ↓ COP.
- Diuretic-induced acid-base and electrolyte imbalance may impair cardiac function.
- Diuretic-induced **hypokalemia** can predispose to digitalis toxicity and cardiac arrhythmia.

Recommendation: Combination between a K^+ sparing diuretic and loop diuretic is the best choice.

CHRONIC KIDNEY DISEASES

The majority of patients with chronic renal diseases (e.g. chronic renal failure, diabetic nephropathy, etc.) have fluid retention, hypertension, hyperkalemia, and acidosis.

Advantages of diuretics:

- Correction of fluid retention.
- Reduction of hyperkalemia.
- Reduction of hypertension.

Recommendation: Loop diuretics are best choice.

Disadvantages of diuretics:

- Thiazides are **ineffective** when GFR is <30 ml/min, moreover it may be harmful.
- K^+ sparing diuretics are **contraindicated** because they can exacerbate hyperkalemia and acidosis.
- Carbonic anhydrase inhibitors (acetazolamide) are **contraindicated** because they can exacerbate acidosis.

LIVER CIRRHOSIS

Patients with chronic liver disease have fluid retention, ascites, hyperammonemia and 2ry hyperaldosteronism.

Advantages of diuretics:

- Correction of fluid retention.
- Spironolactone antagonizes aldosterone.

Disadvantages of diuretics:

- Aggressive use of diuretics can precipitate hepatorenal syndrome.
- Aggressive use of diuretics can precipitate hyperammonemia and hepatic **encephalopathy**. **How?**

- Normally, the urine pH is acidic (~5.6). In acidic urine, most of the absorbable **ammonia** (NH3) is converted into the non-absorbable **ammonium** ions (NH4+) and so it is removed out by the kidney (this is known as ammonia trapping).

- Diuretics cause hypokalemia and metabolic alkalosis. This leads to:
  - Systemic alkalosis causes the pH of the urine to become less acidic. This decreases conversion of the urinary absorbable NH3 into the non-absorbable NH4. The excreted NH3 is thus reabsorbed again from urine to blood → **hyperammonemia**.
  - Systemic alkalosis increases the **entry** of NH3 into the brain cells.

Hepatorenal syndrome

- Functional oliguric RF occurring in a patient with advanced liver disease in absence of other causes of RF. The renal histology is normal.
- The pathogenesis of HRS is not fully understood. Disturbance in renal hemodynamics due to imbalance between renal VC and VD mechanisms may be responsible.
- Prognosis is poor.

Recommendation:
Aldosterone antagonists such as spironolactone are suitable choice in hepatic patients to help prevent the formation of ascites. A loop diuretic may need to be added in refractory cases.

LOWER LIMB EDEMA DURING PREGNANCY

- Lower limb edema during late pregnancy is common condition and is usually benign (physiologic). It occurs due to hormonal imbalance, and compression of pelvic veins by the enlarged uterus.
- Unilateral leg edema, redness, warmth, and tenderness require evaluation for deep venous thrombosis (DVT).
- Physiologic edema can be reduced by elevating the lower extremities and wear elastic stockings.

– Diuretics are better avoided during pregnancy because they effectively **reduce maternal plasma volume** and consequently may reduce amniotic fluid and/or placental blood flow.

Part 4: Volume depletion and fluid replacement

- Volume depletion can be caused by loss of blood or other body fluids e.g. vomiting, diarrhea, etc.
- In cases of mild volume depletion, resuscitation can be adequately achieved with oral fluid alone. Sodium chloride tablets and electrolyte-containing solutions are often used.
- In cases of severe dehydration, i.v. fluid therapy is preferred and may be life-saving.
- Water alone is not an appropriate fluid for volume resuscitation since it enters the cells by osmotic effect. Only one third of each administered liter remains in the extracellular space, and only one twelfth of each administered liter remains in the intravascular space.
- When electrolyte disturbances are present, the fluid used for resuscitation should be chosen to correct both volume depletion and electrolyte disturbances.

Crystalloid solutions

- **Sodium chloride solutions:**

– **Normal saline (0.9% NaCl):** It is the most commonly used solution. It contains 154 mEq sodium per litre, a concentration similar to the sodium concentration of plasma. Due to the relatively high chloride content, normal saline carries a risk of inducing hyperchloraemic metabolic **acidosis** when given in large amounts.

– **Hypotonic saline (0.45% NaCl):** contains 77 mEq sodium per liter, and can be used when there is dehydration with hypernatraemia. In these patients, 5% dextrose in water can be given simultaneously with normal saline.

– **Hypertonic saline (3% NaCl):** contains 513 mEq sodium per liter, and can be used for management of acute hyponatremia.

- **Lactated Ringer's solution:**

– It is an isotonic solution containing sodium, potassium, chloride, calcium and lactate. The lactate is metabolized by the liver into bicarbonate, which can help correct metabolic **acidosis**. In lactic acidosis and **liver disease** this conversion is impaired, so lactate-containing fluids should be avoided.
– It is **not suitable for maintenance** therapy because the Na^+ and K^+ contents are too low to compensate for daily electrolyte requirement.

- **Glucose (Dextrose) solutions:**

– Various concentrations are available e.g. 5%, 10% and 25%. The 5% dextrose in water (also known as D5W) is isotonic and is the most commonly used.
– Hypertonic glucose solutions (above 5%) should be infused very slowly and cautiously to avoid **hyperosmolar syndrome** and life-threatening **dehydration**.

Colloid solutions

– Colloids are classified as either natural (**albumin** and **fresh frozen plasma**) or artificial (**starch** and **dextran**).
– They preserve a high colloid **osmotic pressure** in the blood and theoretically designed to increase the intravascular volume with much less effect on tissue water. However, colloid solutions are a less-preferred choice for the management of volume depletion because they are very expensive and have not shown a mortality benefit over isotonic saline.

Oral rehydration therapy (ORT)

– Oral electrolyte solutions are used in **children**, particularly with gastroenteritis. This product contains sodium, potassium, chloride, citrate, and dextrose, and is designed to replace the electrolytes and water that are lost with vomiting or diarrhea.
– Glucose is typically added to these oral replacement solutions to promote uptake of sodium via the intestinal sodium/glucose co-transporter mechanism.

Part 5: Disorders of serum sodium and potassium

Hyponatremia and SIADH

Normal serum Na^+ is **135-145** mEq/L

- Hyponatremia is defined as serum Na^+ <135 mEq/L. It can be caused by any medical illnesses, such as CHF, liver failure, renal failure, pneumonia, or SIADH.
- Severe hyponatremia (Na^+ <120 mEq/L) leads to fall of plasma osmolality, with movement of water from plasma to brain and other cells causing neurological manifestations (altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, coma or seizures).
- ADH (or vasopressin) is released from posterior pituitary in response to high plasma osmolality. It binds to three receptors: **V1a** in the vasculature (VC), **V1b** in the brain, and **V2** in renal collecting ducts (↑ water absorption).
- When the ADH system is working properly, 'the urine should reflect the blood', i.e. concentrated urine occurs when plasma osmolality is high, and vice versa.

- Many factors (including drugs and other non-pharmacological conditions) can stimulate release of ADH irrespective of plasma osmolality, leading to **hyponatremia**, a condition known as **"syndrome of inappropriate ADH secretion"** or **SIADH.**

Drugs that cause SIADH:
Carbamazepine
Chloropropamide
Cytotoxic drugs
Opiates

Management of SIADH

- **Fluid restriction** (1L/d) is the main line.
- **Demeclocycline** and **lithium** may be "rarely" used; they impair the response of the collecting ducts to ADH (by a non-receptor mechanism).
- **Vasopressin receptor antagonists: "Vaptans":**
  - Antagonism of the V2 receptors results in aquaresis, a unique electrolyte-free water excretion by the kidneys.
  - **Conivaptan** is a mixed V1a and V2 antagonist, and **tolvaptan**, a selective V2 antagonist.
  - **Tolvaptan** is approved for treating hyponatremia associated with heart failure, cirrhosis, and SIADH.
  - Recent studies showed that vaptans may be more effective in treating hypervolemia in heart failure than diuretics.

Hypernatremia

- Hypernatremia is defined as a plasma Na^+ >145 mEq/L, and represents a state of hyperosmolality
- Hypernatremia may be caused by a primary **Na+ gain** or a **water loss**, the latter being much more common. **Renal water loss** results from either **osmotic diuresis** or **diabetes insipidus (DI)**.
- Hypernatremia results in contraction of brain cells as water shifts to attenuate the rising ECF osmolality. Thus, the most severe symptoms of hypernatremia are neurological manifestations.

N.B.

Aggressive correction of hyper- or hyponatremia is potentially dangerous. The rapid shift of water into- or- from brain cells increases the risk of seizures or permanent neurologic damage.

Management of symptomatic hypernatremia

- The mainstay of management is the administration of **water**, preferably by mouth or nasogastric tube. Alternatively, 5% dextrose in water (D5W) can be given intravenously.
- Specific therapy of the underlying cause.

Hypokalemia

Normal serum K^+ is 3.5-5 mEq/L

- Potassium is the major intracellular cation. 98% of K^+ in the body is found in the intracellular compartment, leaving 2% in extracellular fluid spaces.
- Renal K^+ excretion occurs from the DCT and is mediated by aldosterone and Na^+ delivery to the distal nephron.
- Hypokalemia is defined as serum K^+ <3.5 mEq/L. It can result from diminished K^+ intake, transcellular shift of K^+, or increased K^+ loss.
- The most common **manifestations** are muscle weakness, cramps, flattened T wave and prolonged QT interval in the ECG.
- Because K^+ is usually exchanged with H^+ at the DCT, hypokalemia is often linked to metabolic alkalosis. Anyone of these two conditions can lead to the other.

Drugs cause transcellular shift of K^+ (from plasma to tissue):
Insulin and beta-2 agonists: they ↑ transmembrane Na^+/K^+-ATPase activity.

Drugs cause renal loss of K^+:
Mineralocorticoids, glucocorticoids, diuretics, amphotericin-B.

Drugs cause GIT loss of K^+: laxatives

Management

- Patients with a K^+ level of **2.5-3.5** mEq/L may need only oral K^+ replacement
- If the K^+ level **< 2.5** mEq/L, intravenous K^+ should be given. The rate of infusion should not exceed 20 mEq/hr, Rapid IV infusion may cause serious arrhythmia or even cardiac arrest.
- Hypomagnesemia is frequently associated with hypokalemia. Concomitant magnesium deficiency aggravates hypokalemia and renders it difficult to treatment by K^+ alone.

Hyperkalemia

- Hyperkalemia is defined as serum K^+ >5 mEq/L. It can result from transcellular shift of K^+, or decreased renal excretion of K^+ (as in chronic renal failure).
- The most common **manifestations** are muscle paralysis, palpitations, high peaked T wave and short QT interval in the ECG.
- Because K^+ is usually exchanged with H^+ at the DCT, hyperkalemia is often linked to metabolic acidosis.

Drugs cause transcellular shift of K^+ (from tissue to plasma):
Insulin deficiency and β-blockers: they ↓ transmembrane Na^+/K^+-ATPase activity.

Drugs that ↓ renal excretion of K^+:
K+ sparing diuretics, ACEIs, NSAIDs, cyclosporins.

Management

- **Mild hyperkalemia:** could be corrected by diuretics and oral cation exchange resins (Polystyrene sulfonate) to promote the exchange of Na^+ for K^+ in the GIT.
- **Severe hyperkalemia with ECG changes:**
  - Intravenous calcium gluconate to reduce cardiac toxicity (↓ membrane excitability). The usual dose is 10 mL of a 10% solution infused over 2 to 3 minutes.
  - Intravenous insulin with glucose: 20 U regular insulin mixed with 500 ml D5W.
  - Correct metabolic acidosis with i.v. NaHCO3 solution.
  - Hemodialysis is reserved for patients with renal failure or with life-threatening hyperkalemia resistant to other treatment.

Part 6: Pharmacological manipulation of the urine pH

Normal urine pH is 5.2-6.5. It is possible, by the use of pharmacological agents, to produce urinary pH values ranging from ~ 5 to 8.5.

Alkalinization of the urine

- **Indications:**
  - To enhance excretion of acidic drugs and organic compounds e.g. aspirin, sulfonamides, and uric acid.
  - To enhance dissolution of uric acid and cystine stones.
  - To relieve dysuria (burning micturition) in some cases of bladder infection.
- **Alkalinizing agents:**
  - **Oral:** sodium and potassium citrate salts: citrate is metabolized into bicarbonate which is excreted in urine.
  - **Intravenous** bicarbonate solution: contains 5% NaHCO3.

Acidification of the urine

- **Indications:**
  - It is rarely used clinically except in a specialized test to discriminate between different kinds of renal tubular acidosis.
  - It can be very dangerous in cases of renal or hepatic impairment.
- **Acidifying agents:**
  - **Oral:** ascorbic acid > 2 g/d.
  - **Intravenous** ammonium chloride (NH4Cl) solution.

Notes

Notes

Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Furosemide in arterial hypertension.
- Furosemide in acute pulmonary edema.
- Thiazides in diabetes insipidus.

Mention the pharmacodynamic principles underlying the contraindication of:

- Furosemide in acute hyperuricemia.
- Thiazides in uncontrolled diabetes mellitus.
- Spironolactone in chronic renal failure.
- Amiloride with ACEIs.
- Ethacrynic acid with aminoglycosides.
- Furosemide with NSAIDs.

Mention the advantages and disadvantages of diuretics in the following conditions:

- Congestive heart failure.
- Chronic kidney disease.
- Chronic liver disease.

Mention the rational of the following combination:

- Furosemide with spironolactone.

Mention 3 differences between:

- Furosemide and spironolactone.

Of each of the following questions, select THE ONE BEST answer:

1. The ascending part of the loop of Henle is the principal site of action of the following diuretics:
A. Hydrochlorothiazide
B. Triamterine
C. Amiloride
D. Bumetanide
E. Spironolactone

2. Hyperkalemia is a contraindication of the following diuretics:
A. Furosemide
B. Bumetanide
C. Ethacrynic acid
D. Chlorothiazide
E. Spironolactone

3. Loop diuretics are clinically useful in the treatment of all the following edematous states EXCEPT:
A. Edema caused by congestive heart failure
B. Edema caused by chronic liver failure
C. Lymphedema
D. Nephrotic syndrome
E. Ankle edema due to chronic hydralazine treatment

4. Intravenous albumin is the ideal choice for treatment of the following conditions:
A. Ascites due to chronic liver disease
B. Edema due to chronic kidney disease
C. Edema due to congestive heart failure
D. Lymphedema
E. Inflammatory edema

5. Vigorous diuretics are contraindicated in resistant ascites due advanced liver disease because:
A. It can lower blood pressure to a critical level
B. It can precipitate hepatorenal syndrome
C. It can lead to severe dehydration
D. It can decrease ascetic fluid suddenly and drastically
E. It aggravate hypoalbuminemia

6. Which of the following diuretics can enhance the parathormone-mediated calcium reabsorption from the distal renal tubules:
A. Hydrochlorothiazide
B. Triamterine
C. Amiloride
D. Bumetanide
E. Spironolactone

7. Idiopathic calcium urolithiasis (hypercalciuria) can be treated by:
A. Hydrochlorothiazide
B. Ethacrynic acid
C. Furosemide
D. Triamterine
E. Bumetanide

8. Spironolactone is characterized by:
A. It interferes with aldosterone synthesis
B. It competitively inhibit aldosterone action in the distal part of the distal renal tubules
C. It inhibits sodium reabsorption in the proximal renal tubules
D. It is more potent diuretic than hydrochlorothiazide
E. It has rapid onset and short duration

9. Hydrochlorothiazide is clinically useful in the treatment of all the following conditions EXCEPT:
A. Edema caused by congestive heart failure
B. Edema caused by chronic liver failure
C. Edema caused by chronic renal failure
D. Hypertension with or without edema
E. Recurrent calcium urolithiasis

10. Adverse reactions associated with thiazide therapy include all the following EXCEPT:
A. Hyperglycemia
B. Hyperuricemia
C. Metabolic acidosis
D. Fluid and electrolyte imbalance
E. Hypotension

11. All the following diuretics can aggravate digitalis toxicity EXCEPT:
A. Hydrochlorothiazide

B. Furosemide
C. Bumetanide
D. Amiloride
E. Ethacrynic acid

12. Adverse effects of loop diuretics include all the following EXCEPT:
A. Magnesium deficiency
B. Sodium deficiency
C. Hypoglycemia
D. Hypovolemia
E. Hyperuricemia

13. Hypokalemia can be caused by all the following drugs EXCEPT:
A. Captopril
B. Salbutamol
C. Thiazides
D. Corticosteroids
E. Insulin

14. The following statements are true concerning the precautions during the use of diuretics in different metabolic disorders EXCEPT:
A. Furosemide may enhance digitalis toxicity in congestive heart failure
B. Furosemide may aggravate hyperammonemia in chronic liver failure
C. Chlorothiazides may aggravate renal impairment in chronic renal failure
D. Thiazides may aggravate hyperglycemia in diabetes mellitus
E. Thiazides may increase formation of urinary uric acid crystals in chronic gout

15. All the following drugs can produce salt and water retention after their prolonged use EXCEPT:
A. Nifedipine
B. Minoxidil
C. Amiloride
D. Prazosin
E. Hydralazine

16. Adverse reactions associated with furosemide therapy include all the following EXCEPT:
A. Hearing loss
B. Hyperuricemia
C. Metabolic alkalosis
D. Fluid and electrolyte imbalance
E. Hypercalcemia

17. Acute pulmonary edema is best treated by i.v. administration of:
A. Hydrochlorthiazide
B. Furosemide
C. Mannitol
D. Amiloride
E. Metalozone

18. Which of the following diuretics has the highest potential to cause ototoxicity:
A. Chlorothiazide
B. Furosemide
C. Ethacrynic acid
D. Acetazolamide
E. Spironolactone

19. All the following are uses of loop diuretics EXCEPT:
A. Acute pulmonary edema
B. Severe hypertension
C. Acute hypercalcemia
D. Acute oliguria
E. Calcium urolithiasis

20. In an addisonian patient, all of the following agents would have diuretic action EXCEPT:
A. Mannitol
B. Chlorothiazide.
C. Bumetanide
D. Furosemide.
E. Spironolactone

21. Gynecomastia may occur with the use of the following diuretics:
A. Chlorothiazide
B. Furosemide
C. Amiloride
D. Acetazolamide
E. Spironolactone

22. The most dangerous complication of injudicious use of diuretics in patients with advanced liver diseases is:

A. Aggravation of hypotension and fatigue
B. Electrolyte imbalance
C. Acid-base imbalance
D. Precipitation of hepatorenal syndrome
E. Marked dehydration

23. Acute congestive glaucoma is best treated by i.v. administration of:
A. Bumetanide
B. Furosemide
C. Mannitol
D. Amiloride
E. Metalozone

24. The following statements concerning hypokalemia are true EXCEPT:
A. It is a side effect predicted with all diuretics
B. It is commonly seen in patients with hyperaldosteronism
C. It can be manifested by ECG changes
D. It could be prevented by the use of K+ sparing diuretics
E. It is a risk factor for digitalis toxicity

25. The best intravenous agent given to patients with advanced liver disease to correct ascites and edema is:
A. Human albumin
B. Mannitol
C. Furosemide
D. Chlorothiazide
E. Spironolactone

26. A 63-year-old man presents to the emergency department with worsening heart failure. Physical exam reveals pitting edema in his ankles. Past medical history is significant for an allergic reaction following exposure to trimethoprim–sulfamethoxazole. Which drug should the physician prescribe to him?
A. Acetazolamide
B. Ethacrynic acid
C. Hydrochlorothiazide
D. Mannitol
E. furosemide

27. A 64-year-old woman with congestive heart failure. She complains of swelling in her legs and ankles. The doctor decides to increase her level of diuretics. What complication should the doctor be most aware of for this patient?
A. Diuretic-induced metabolic acidosis
B. Hepatic encephalopathy
C. Hypercalcemia
D. Hyperkalemia
E. Hypokalemia

28. One of your clinic patients is being treated with spironolactone. Which of the following statements best describes a property of this drug?
A. Contraindicated in heart failure, especially if severe
B. Inhibits Na+ reabsorption in the proximal renal tubule of the nephron
C. Interferes with aldosterone synthesis
D. Is a rational choice for a patient with an adrenal cortical tumor
E. Is more efficacious than hydrochlorothiazide in all patients who receive the drug

29. A patient taking an oral diuretic for about 6 months presents with elevated fasting and postprandial blood glucose levels. You suspect the glycemic problems are diuretic-induced. Which of the following was the most likely cause?
A. Acetazolamide
B. Amiloride
C. Chlorothiazide
D. Spironolactone
E. Triamterene

30. Chlorthalidone and torsemide are members of different diuretic classes, in terms of mechanisms of action, but they share the ability to cause hypokalemia. Which of the following statements best describes the general mechanism by which these drugs cause their effects that lead to net renal loss of potassium?
A. Act as aldosterone receptor agonists, thereby favoring K+ loss

B. Block proximal tubular ATP-dependent secretory pumps for K+
C. Increase delivery of Na+ to principal cells in the distal nephron, where tubular Na+ is transported into the cells via a sodium channel in exchange for K+, which gets eliminated in the urine
D. Inhibit a proximal tubular Na,K-ATPase such that K+ is actively pumped into the urine
E. Lower distal tubular urine osmolality, thereby favoring passive diffusion of K+ into the urine

31. Which of the following is a clinical indication for use of Mannitol?
A. Chronic simple glaucoma
B. Cerebral edema
C. Pulmonary edema
D. Acute heart failure
E. chronic renal failure

32. All the diuretics act from the luminal side of the renal tubule EXCEPT:
A. Torsemide
B. Hydrochlorothiazide
C. Spironolactone
D. Chlorthalidone
E. Furosemide

33. A 55-year-old male with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks, he develops an attack of gout. Which diuretic was he taking?
A. Furosemide.
B. Hydrochlorothiazide.
C. Spironolactone.
D. Triamterene
E. Acetazolamide

34. Your 60 year old male hypertensive patient who had a myocardial infarction a year ago is now showing signs of CHF. You therefore add spironolactone to his drug regimen. What side effect should you warn him about?
A. Gynecomastia
B. Hypokalemia
C. Lupus
D. Ototoxicity
E. Hyperuricemia

Answers

1 D	11 D	21 E	31 B
2 E	12 C	22 D	32 C
3 C	13 A	23 C	33 B
4 A	14 E	24 A	34 A
5 B	15 C	25 A	
6 A	16 E	26 B	
7 A	17 B	27 E	
8 B	18 C	28 D	
9 C	19 E	29 C	
10 C	20 E	30 C	

Table of Contents

CHAPTER 4: AUTACOIDS AND ANTI-INFLAMMATORY DRUGS

CHAPTER 5: CARDIOVASCULAR PHARMACOLOGY